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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,705	04/17/2001	Yuki Abe	01149/HG	7090

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EXAMINER

KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/836,705	Applicant(s) ABE ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-68 is/are pending in the application.
- 4a) Of the above claim(s) 1-39, 44 and 46-55 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 40-43, 45, 56-64 and 66-68 is/are rejected.
- 7) ☒ Claim(s) 65 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/8/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. In response to a previous Office action, a Final rejection (mailed on January 16, 2004), Applicants filed an after-final amendment on April 8, 2004, previously not entered (see Advisory action mailed April 22, 2004), which is now entered by virtue of Applicant's request for continued examination (RCE) filed on April 28, 2004. Said amendment amended Claims 40, 42, 43, and 56 and added new Claims 61-66. A supplemental amendment filed April 28, 2004 added new Claims 67-68. Thus, Claims 1-68 are pending herein.

Election/Petition

2. Applicants' petition of the restriction requirement, filed on October 8, 2003, which restriction was made final in a previous Office action, is noted. Said petition was denied in a paper mailed on March 18, 2004.

Claims 1-68 are pending in the instant application. Claims 1-39, 44, and 46-55 are withdrawn from consideration as non-elected inventions. Claims 40-43, 45, and 56-68 will be examined herein.

Priority

3. As previously noted, the instant application is granted the benefit of priority for the foreign application 2000-116591 filed in Japan on April 18, 2000 and 2000-117458 filed in Japan on April 19, 2000 as requested in the declaration. Receipt was previously acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are not in English; no English translations have been filed.

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Information Disclosure Statement

4. The information disclosure statement originally filed on October 25, 2001 and refiled on April 8, 2004 has been considered. The two documents, Matsuoka *et al.* and Shiao *et al.*, have now been considered as evidenced by the Examiner's initials on the attached copy.

Withdrawn - Objections to the Specification

5. Previous objection to the Abstract for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)) is withdrawn by virtue of Applicant's amendment filed on October 8, 2003.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

6. Previous rejection of Claims 40-43, 45 and 56-60 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using host cells that contain the biosynthetic pathway for ML-236B (for example, *P. citrinum*), does not reasonably provide enablement for methods using host cells that do not contain the biosynthetic pathway for ML-236B is withdrawn by virtue of Applicant's amendment requiring the host cell of the method to produce ML-236B prior to transformation. Applicant's arguments filed April 8, 2004 are moot in view of the instant withdrawal of the rejection.

7. Previous rejection of Claims 56-58 under 35 U.S.C. § 112, first paragraph, enabling deposit, is withdrawn by virtue of Applicant's amendment to the specification to include the full address of the depository.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

8. Previous rejection of Claims 40, 45, and 60 under 35 U.S.C. § 102(a) as being anticipated by WO 2001/12814 is withdrawn by virtue of Applicant's amendment to Claim 40 and the vector used.

NEW ISSUES

Claim Objections

9. Claim 43 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The language of Claim 40, the parent claim, requires the vector not encode any one of mlcA-E while the instant claim requires that the method occur in the absence of a recombinant gene encoding any one of mlcA-E. Since any recombinant gene is broader than a vector-encoded gene, Claim 43 implies a broader limitation than Claim 40.

10. Applicant is advised that should claim 56 be found allowable, claim 58 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k). Both Claims 56 and 58 are drawn to methods of making ML-236B using pSAKexpR.

11. Applicant is advised that should claim 41 be found allowable, claim 59 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. When two claims in an

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application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k). Because the phrase “consists of” cannot close the language of Claim 40, due to the vector construction (see rejection under 35 U.S.C. § 112, second paragraph, below), the understanding of the language of Claim 59 is identical to that of Claim 41 in scope.

12. Applicant is advised that should claim 64 be found allowable, claim 66 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k). Both claims require the absence of the same recombinant genes in the same method.

13. Claim 65 is objected to for depending from a rejected claim.

New - Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 59 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The requirement of the polynucleotide to consist of a particular sequence when it is a part of the vector of Claim 40 is confusing. Clarification is required.

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The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 40-43, 45, 59-64, and 66-68 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The exclusion of mlcE, either by encoding SEQ ID NO:38 or by exactly SEQ ID NO:37, is considered new matter. While the Examiner can find support for the exclusion of mlcA-D (see original claim 43, for example), no support for excluding mlcE can be identified. Applicant is required to either cite clear support (page and line number) in support of the alleged new matter or cancel the alleged new matter.

16. Claims 40-43, 45, 56-60, 62-64, and 66 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant rejection is specifically recited against “a host cell which is a ML-236B producing micro-organism which belongs to the *Penicillium* genus” as found in Claims 40 and 56.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics,

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functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

In the specification, three examples of *Penicillium* species that produce ML-236B are found in the specification (see page 9); however, this list is not indicated as a complete list. The art contains numerous examples of *Penicillium* species. The instant claims are drawn to methods using a *subgenus* of all *Penicillium*, wherein the *Penicillium* must produce ML-236B. The specification does not describe *Penicillium* host cells that produce ML-236B to the exclusion of *Penicillium* host cells that do not produce said antibiotic. The specification does not link the structural requirements of *Penicillium* host cells needed for the noted function. Thus, the claimed subgenus does not have adequate written description.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 40, 42, 43, 45, 60, 61, 63, 64, and 66-68 are rejected under 35 U.S.C. § 103(a) as being obvious over **Abe *et al.*** (WO 01/12814, published February 22, 2001 - see IDS filed June 10, 2003) in view of **Yu *et al.*** (Applied and Environmental Microbiology (1995) 61(6): 2365-2371) and further in view of **Chang *et al.*** (Applied and Environmental Microbiology (1995) 61(6): 2372-2377). The instant claims are drawn to making ML-236B or pravastatin using a

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Penicillium host cell (*P. citrinum*, *P. brevicompactum*, and *P. cyclopium*) transformed with genomic *mlcR* that encodes SEQ ID NO:42, wherein said vector does not contain DNA encoding any one of *mlcA-E*.

Abe *et al.* teach methods of improving production of ML-236B and pravastatin in host cells *P. citrinum*, *P. brevicompactum*, and *P. cyclopium* by transforming said host cells with genomic DNA encoding *mlcA-E* and *mlcR* (see abstract, page 11, page 55, and Figure 3); said DNA encodes six proteins, one of which is identical to SEQ ID NO:42 in the instant application (see previously attached alignment). While Abe *et al.* do not expressly teach transforming said host cells with each of the disclosed genes individually [incidentally, a common practice in the art], Abe *et al.* do analogize the disclosed gene cluster for ML-236B with other polyketide synthase gene clusters, such as for aflatoxin biosynthesis (see page 2).

Yu *et al.* teach the gene cluster for aflatoxin, which cluster contains the regulatory gene *aflR* (see Figure 1).

Chang *et al.* teach overexpression of *aflR* on a vector independent of other aflatoxin biosynthesis genes for the increased production of aflatoxin (see abstract and page 2376, right column).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to overexpress *mlcR* alone to produce ML-236B and pravastatin in *Penicillium* host cells because the distinct genomic open reading frames are taught by Abe *et al.* and, via their analogy to aflatoxin genes, overexpression of the “R” gene is productive in affecting biosynthesis from the enzymes encoded by the gene cluster. One would have been motivated to practice the claimed invention because pravastatin, and its precursor ML-236B, are commercially useful

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products (see page 1 of Abe *et al.*). One would have had a reasonable expectation of success that overexpression of *mlcR* alone in *Penicillium* would produce ML-236B because expression of all of *mlcA-E* and *mlcR* in *Penicillium* produces ML-236B (see Abe *et al.*, Abstract) and there is no indication in the art, particularly via analogy with other polyketide synthase clusters as discussed by Abe *et al.*, that expression of just *mlcR* would abolish ML-236B production – on the contrary, an increase in production is indicated by analogy although no such increase is a required limitation in the claims.

Summary of Pending Issues

18. The following is a summary of the issues pending in the instant application:

- a) Claim 43 stands objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.
- b) Claim 58 is noted as being a duplicate of Claim 56.
- c) Claim 59 is noted as being a duplicate of Claim 41.
- d) Claim 65 stands objected to for depending from a rejected claim.
- e) Claim 66 is noted as being a duplicate of Claim 64.
- f) Claim 59 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for being open or closed with respect to the polynucleotide of the vector in the method.
- g) Claims 40-43, 45, 59-64, and 66-68 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.
- h) Claims 40-43, 45, 56-60, 62-64, and 66 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
- i) Claims 40, 42, 43, 45, 60, 61, 63, 64, and 66-68 stand rejected under 35 U.S.C. § 103(a) as being obvious over Abe *et al.* in view of Yu *et al.* and further in view of Chang *et al.*

Conclusion

19. Claim 65 is objected to; Claims 40-43, 45, 56-64, and 66-68 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the

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objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931.

The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Examiner
Art Unit 1652

June 28, 2004